Aus der Klinik für Radioonkologie und Strahlentherapie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Akzelerierte hyperfraktionierte Radiotherapie plus Temozolomid beim Glioblastom

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Julian Gabriel Florange

aus Hannover

Datum der Promotion: 16.06.2018

Inhaltsverzeichnis

1 Abstrakt

Einführung:

Gliome sind die häufigsten primären Tumoren des zentralen Nervensystems bei Erwachsenen. Der häufigste und bösartigste Typ der Gliome ist das Glioblastom. Derzeitige Behandlungsstandards bestehen aus Resektion, adjuvanter normal fraktionierter Radiotherapie mit gleichzeitiger Gabe von Temozolomid und Temozolomid Gabe nach Radiotherapie. Hyperfraktionierte Radiotherapien oder hyperfraktionierte akzelerierte Radiotherapien (HART) werden aufgrund einer hypothetischen Reduktion später Bestrahlungsschäden sowie einer Verhinderung der Repopulation des Tumorbetts diskutiert.

Die hyperfraktionierte Radiotherapie und die HART wurden vor Einführung von Temozolomid als Standard in der Chemotherapie des Glioblastoms ausgiebig untersucht, ohne eindeutige Ergebnisse. In dieser Studie untersuchten wir die Rolle der hyperfraktionierten akzelerierten Radiotherapie in der Temozolomid Ära.

Material und Methoden:

Wir verglichen für den Behandlungszeitraum von Februar 2009 bis Oktober 2014 64 Patienten, behandelt mit HART, mit 67 Patienten, die mit klassischer, normal fraktionierter Radiotherapie (RT) behandelt wurden. 62 der mit einer HART behandelten und 64 der mit klassischer RT behandelten Patienten erhielten Temozolomid. Follow-up Daten wurden bis Januar 2015 analysiert.

Ergebnisse:

Das mediane Overall Survival (OS) betrug 13 Monate für alle Patienten. Für mit klassischer RT behandelte Patienten betrug das mediane OS 15 Monate, für mit HART behandelte Patienten 10 Monate. In der univariablen und multivariablen Analyse besaß das Regime der Fraktionierung keinen Vorhersagewert für das Überleben.

Diskussion:

In der univariablen und multivariablen Analyse ließen sich keine signifikanten Unterschiede zwischen den klassischen RT und HART Regimen nachweisen. Die Vorzüge sind offenkundig: das akzelerierte Regime verkürzt bedeutsam die Dauer der Hospitalisierung für ein Patientenkollektiv mit stark eingeschränkter Lebenserwartung. Wir schlagen eine weitere Untersuchung der Rolle einer HART in Kombination mit Temozolomid in zukünftigen prospektiv angelegten Studien vor.

(Kaul, D., et al., Accelerated hyperfractionation plus temozolomide in glioblastoma. Radiat Oncol, 2016. 11: p. 70)

2 Abstract

Introduction:

Gliomas are the most common primary tumors of the central nervous system in adults. The most common and most malignant type of glioma is glioblastoma. Current standard of care comprises resection, adjuvant normofractionated radiotherapy with concurrent temozolomide and post-RT temozolomide. Hyperfractionated (HFRT) or accelerated hyperfractionated radiotherapy (AHFRT) have been discussed based on a hypothesized reduction of late radiation injury and prevention of repopulation. HFRT and AHFRT have been examined extensively in the pre-Temozolomide era with inconclusive results. In this study we examined the role of accelerated hyperfractionation in the Temozolomide era.

Materials and methods:

Sixty-four patients who underwent AHFRT (62 of which received Temozolomide) were compared to sixty-seven patients who underwent normofractionated (64 of which received Temozolomide) between 02/2009 and 10/2014. Follow-up data were analyzed until 01/2015.

Results:

Median overall survival (OS) was 13 months for all patients. For patients treated with NFRT median OS was 15 months, for patients treated with AHFRT median OS was 10 months. The fractionation regimen was not a predictor of survival in univariable- or multivariable analysis.

Discussion:

Univariable and multivariable analysis did not show significant differences between the NFRT and AHFRT fractionation regimens. The benefits are immanent: the regimen does significantly shorten hospitalization time in a patient collective with a highly impaired life expectancy. We propose that the role of AHFRT in combination with Temozolomide should be further examined in future prospective trials.

(Kaul, D., et al., Accelerated hyperfractionation plus temozolomide in glioblastoma. Radiat Oncol, 2016. 11: p. 70)

3 Eidesstattliche Versicherung

„Ich, Julian Gabriel Florange, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Akzelerierte hyperfraktionierte Radiotherapie plus Temozolomid beim Glioblastom selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -*www.**icmje**.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.
Mein Anteil an der ausgewählten Publikation entspricht dem, der in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben ist.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum _____ Unterschrift

Ausführliche Anteilserklärung an der erfolgten Publikation

Publikation: David Kaul (38%), Julian Florange (38%), Harun Badakhshi (5%), Arne Grün (3%), Pirus Ghadjar (3%), Sebastian Exner (3%), Volker Budach (10%), Accelerated hyperfractionation plus temozolomide in glioblastoma, Radiation Oncology, 2016
Besonderheit: geteilte Erstautorenschaft
Beitrag im Einzelnen:
Die für die Durchführung dieser Studie benötigten Patientendaten wurden von Herrn Florange aus den digitalen Archiven der Charité extrahiert, sortiert und für die statistische Analyse aufbereitet. Die Durchführung der statistischen Analyse erfolgte in Zusammenarbeit mit Herrn Dr. med Kaul. Hierbei führten Herr Florange und Herr Dr. med Kaul parallel die vollständige Analyse und Darstellung der Ergebnisse aus, die doppelte Ausführung der Analysen und der Vergleich der Ergebnisse erfolgten zur Bestätigung der Richtigkeit dieser.
Das Manuskript wurde von Herrn Florange in Kooperation mit Herrn Dr. med Kaul entworfen und verfasst. Herr Florange führte hierzu eine Literaturanalyse durch und wählte geeignete Quellen aus. Des Weiteren konzipierte Herr Florange die erste Fassung des Textes, die Herr Dr. med. Kaul ausformulierte. Im Anschluss korrigierten und überarbeiteten Herr Florange und Herr Dr. med Kaul diese bis zur publizierten Endfassung gemeinsam.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

_____

Unterschrift des Doktoranden

_____

4 Auszug aus der Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2016** Selected Editions: SCIE,SSCI Selected Categories: **"RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"** Selected Category Scheme: WoS

Gesamtanzahl: 126 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JACC-Cardiovascular Imaging	6,895	10.189	0.027050
2	RADIOLOGY	50,983	7.296	0.066140
3	EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	14,019	7.277	0.024910
4	Circulation-Cardiovascular Imaging	4,472	6.803	0.019120
5	JOURNAL OF NUCLEAR MEDICINE	24,977	6.646	0.037540
6	NEUROIMAGE	85,630	5.835	0.173210
7	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	4,349	5.601	0.014950
8	SEMINARS IN RADIATION ONCOLOGY	2,232	5.356	0.003910
9	INVESTIGATIVE RADIOLOGY	5,925	5.195	0.011230
10	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	44,068	5.133	0.060060
11	ULTRASOUND IN OBSTETRICS & GYNECOLOGY	11,611	4.710	0.019350
12	HUMAN BRAIN MAPPING	18,139	4.530	0.041900
13	RADIOTHERAPY AND ONCOLOGY	15,639	4.328	0.028040
14	MEDICAL IMAGE ANALYSIS	5,539	4.188	0.010720
15	EUROPEAN RADIOLOGY	16,381	3.967	0.033340
16	IEEE TRANSACTIONS ON MEDICAL IMAGING	15,215	3.942	0.019660
17	JOURNAL OF NUCLEAR CARDIOLOGY	3,021	3.930	0.003920
18	MAGNETIC RESONANCE IN MEDICINE	29,816	3.924	0.035960
19	CLINICAL NUCLEAR MEDICINE	4,008	3.640	0.006470
20	SEMINARS IN NUCLEAR MEDICINE	2,056	3.630	0.002800
21	AMERICAN JOURNAL OF NEURORADIOLOGY	21,720	3.550	0.032180
22	MOLECULAR IMAGING AND BIOLOGY	2,228	3.466	0.005880
23	ULTRASCHALL IN DER MEDIZIN	1,907	3.452	0.003930
24	RADIOGRAPHICS	10,286	3.427	0.009660
25	Biomedical Optics Express	6,187	3.337	0.021610
26	Contrast Media & Molecular Imaging	1,131	3.307	0.002810
27	INTERNATIONAL JOURNAL OF HYPERTHERMIA	3,030	3.262	0.003810

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
28	Journal of Cardiovascular Computed Tomography	1,331	3.185	0.004220
29	JOURNAL OF MAGNETIC RESONANCE IMAGING	15,073	3.083	0.029170
30	Journal of the American College of Radiology	2,690	2.993	0.006840
31	NMR IN BIOMEDICINE	6,766	2.872	0.014560
32	JOURNAL OF VASCULAR AND INTERVENTIONAL RADIOLOGY	8,371	2.780	0.012840
33	AMERICAN JOURNAL OF ROENTGENOLOGY	31,676	2.778	0.035740
34	PHYSICS IN MEDICINE AND BIOLOGY	22,873	2.742	0.034390
35	STRAHLENTHERAPIE UND ONKOLOGIE	2,687	2.735	0.004990
36	Clinical Neuroradiology	433	2.618	0.001550
37	MEDICAL PHYSICS	22,942	2.617	0.037250
38	Radiation Oncology	4,358	2.568	0.013680
39	RADIATION RESEARCH	8,394	2.539	0.007920
40	JOURNAL OF BIOMEDICAL OPTICS	12,700	2.530	0.024520
41	JOURNAL OF NEURORADIOLOGY	792	2.526	0.001310
42	ULTRASOUND IN MEDICINE AND BIOLOGY	9,759	2.494	0.012640
43	QUARTERLY JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	1,030	2.481	0.001800
44	CLINICAL RADIOLOGY	5,717	2.478	0.008540
45	EUROPEAN JOURNAL OF RADIOLOGY	11,328	2.462	0.026500
46	NUCLEAR MEDICINE AND BIOLOGY	3,918	2.426	0.006210
47	CANCER IMAGING	1,008	2.404	0.001930
48	RADIATION AND ENVIRONMENTAL BIOPHYSICS	1,468	2.398	0.002460
49	ULTRASONICS	5,752	2.327	0.008130
50	Diagnostic and Interventional Imaging	957	2.277	0.002420
51	MAGNETIC RESONANCE IMAGING	6,465	2.225	0.011370
52	CARDIOVASCULAR AND INTERVENTIONAL RADIOLOGY	4,859	2.191	0.008890
53	KOREAN JOURNAL OF RADIOLOGY	1,941	2.156	0.003730
54	ACADEMIC RADIOLOGY	4,804	2.128	0.009150
55	NEURORADIOLOGY	5,191	2.093	0.007520
56	Dose-Response	671	2.088	0.001310
57	Brachytherapy	1,442	2.082	0.003540
58	BRITISH JOURNAL OF RADIOLOGY	7,990	2.050	0.011760
59	EJNMMI Research	844	2.033	0.003380

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
60	ACTA RADIOLOGICA	4,199	2.011	0.006600
61	JOURNAL OF THORACIC IMAGING	1,265	2.010	0.002550
62	INTERNATIONAL JOURNAL OF RADIATION BIOLOGY	4,417	1.992	0.004350
63	Physica Medica-European Journal of Medical Physics	1,385	1.990	0.003530
64	INTERNATIONAL JOURNAL OF CARDIOVASCULAR IMAGING	2,742	1.896	0.007940
65	RADIOLOGIC CLINICS OF NORTH AMERICA	2,330	1.890	0.002560
66	Diagnostic and Interventional Radiology	1,029	1.886	0.002530
67	International Journal of Computer Assisted Radiology and Surgery	1,474	1.863	0.003300
68	ABDOMINAL IMAGING	3,246	1.842	0.006240
69	Radiologia Medica	1,881	1.795	0.003430
70	JOURNAL OF RADIATION RESEARCH	2,270	1.788	0.004620
71	ULTRASONIC IMAGING	1,040	1.780	0.000750
72	COMPUTERIZED MEDICAL IMAGING AND GRAPHICS	1,800	1.738	0.002530
73	SKELETAL RADIOLOGY	5,263	1.737	0.009010
74	MAGNETIC RESONANCE MATERIALS IN PHYSICS BIOLOGY AND MEDICINE	1,391	1.718	0.002840
75	CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS	1,567	1.689	0.002330
76	Radiology and Oncology	604	1.681	0.001500
77	JOURNAL OF NEUROIMAGING	1,772	1.664	0.004420
78	JOURNAL OF RADIOLOGICAL PROTECTION	974	1.657	0.001970
79	DENTOMAXILLOFACIAL RADIOLOGY	2,076	1.594	0.003040
80	JOURNAL OF ULTRASOUND IN MEDICINE	6,094	1.547	0.007920
81	Zeitschrift fur Medizinische Physik	450	1.531	0.001220
82	Journal of Contemporary Brachytherapy	332	1.496	0.000630
83	Molecular Imaging	1,135	1.479	0.001900
84	NUCLEAR MEDICINE COMMUNICATIONS	2,752	1.472	0.004640
85	PEDIATRIC RADIOLOGY	5,489	1.465	0.007820
86	Magnetic Resonance Imaging Clinics of North America	870	1.446	0.001490
87	ROFO-FORTSCHRITTE AUF DEM GEBIET DER RONTGENSTRAHLEN UND DER BILDGEBENDEN VERFAHREN	1,428	1.418	0.002530

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
88	JOURNAL OF DIGITAL IMAGING	1,518	1.407	0.002650
89	ANNALS OF NUCLEAR MEDICINE	1,980	1.396	0.003440
90	JOURNAL OF COMPUTER ASSISTED TOMOGRAPHY	5,549	1.394	0.005280
91	SEMINARS IN MUSCULOSKELETAL RADIOLOGY	705	1.374	0.001340
92	Journal of Applied Clinical Medical Physics	1,775	1.338	0.004390
93	NEUROIMAGING CLINICS OF NORTH AMERICA	1,017	1.325	0.001350
94	HEALTH PHYSICS	4,176	1.276	0.003730
95	CANADIAN ASSOCIATION OF RADIOLOGISTS JOURNAL-JOURNAL DE L ASSOCIATION CANADIENNE DES RADIOLOGISTES	489	1.266	0.000890
96	Journal of Medical Imaging and Radiation Oncology	945	1.189	0.002740
97	SEMINARS IN INTERVENTIONAL RADIOLOGY	863	1.150	0.001480
98	Magnetic Resonance in Medical Sciences	606	1.141	0.001160
99	SEMINARS IN ULTRASOUND CT AND MRI	828	1.130	0.001240
100	APPLIED RADIATION AND ISOTOPES	7,005	1.128	0.008660
101	Journal of Innovative Optical Health Sciences	355	1.120	0.000810
102	Medical Ultrasonography	492	1.118	0.001330
103	NUKLEARMEDIZIN-NUCLEAR MEDICINE	534	1.087	0.000970
104	BMC MEDICAL IMAGING	592	1.060	0.001490
105	SURGICAL AND RADIOLOGIC ANATOMY	2,583	1.051	0.003240
106	Hellenic Journal of Nuclear Medicine	347	1.048	0.000570
107	CLINICAL IMAGING	1,684	1.015	0.003420
108	Japanese Journal of Radiology	797	0.982	0.002260
109	Medical Dosimetry	687	0.957	0.001110
110	Revista Espanola de Medicina Nuclear e Imagen Molecular	386	0.951	0.000720
111	Cancer Radiotherapie	780	0.930	0.001060
112	RADIATION PROTECTION DOSIMETRY	5,723	0.917	0.007160
113	JOURNAL OF CLINICAL ULTRASOUND	2,012	0.906	0.001950
114	Ultrasound Quarterly	461	0.902	0.000790
115	INTERVENTIONAL NEURORADIOLOGY	900	0.739	0.001590
116	SEMINARS IN ROENTGENOLOGY	423	0.667	0.000500

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
117	Journal of Medical Imaging and Health Informatics	401	0.621	0.000670
118	Iranian Journal of Radiology	193	0.554	0.000590
119	Journal of Medical Ultrasonics	243	0.455	0.000410
120	RADIOLOGE	498	0.404	0.000480
121	RADIOPROTECTION	285	0.388	0.000380
122	Current Medical Imaging Reviews	269	0.308	0.000580
123	JBR-BTR	262	0.252	0.000470
124	International Journal of Radiation Research	57	0.250	0.000110
125	Journal of the Belgian Society of Radiology	5	0.027	0.000010
126	Abdominal Radiology	64	Not Available	0.000000

Radiation Oncology

RESEARCH Open Access

Accelerated hyperfractionation plus temozolomide in glioblastoma

David Kaul*†, Julian Florange†, Harun Badakhshi, Arne Grün, Pirus Ghadjar, Sebastian Exner and Volker Budach

Abstract

Introduction: Hyperfractionated (HFRT) or accelerated hyperfractionated radiotherapy (AHFRT) have been discussed as a potential treatment for glioblastoma based on a hypothesized reduction of late radiation injury and prevention of repopulation. HFRT and AHFRT have been examined extensively in the pre-Temozolomide era with inconclusive results. In this study we examined the role of accelerated hyperfractionation in the Temozolomide era.

Materials and methods: Sixty-four patients who underwent AHFRT (62 of which received Temozolomide) were compared to 67 patients who underwent normofractionated radiotherapy (NFRT) (64 of which received TMZ) between 02/2009 and 10/2014. Follow-up data were analyzed until 01/2015.

Results: Median progression-free survival (PFS) was 6 months for the entire cohort. For patients treated with NFRT median PFS was 7 months, for patients treated with AHFRT median PFS was 6 months. Median overall survival (OS) was 13 months for all patients. For patients treated with NFRT median OS was 15 months, for patients treated with AHFRT median OS was 10 months. The fractionation regimen was not a predictor of PFS or OS in univariable- or multivariable analysis. There was no difference in acute toxicity profiles between the two treatment groups.

Conclusions: Univariable and multivariable analysis did not show significant differences between NFRT and AHFRT fractionation regimens in terms of PFS or OS. The benefits are immanent: the regimen does significantly shorten hospitalization time in a patient collective with highly impaired life expectancy. We propose that the role of AHFRT + TMZ should be further examined in future prospective trials.

Introduction

Gliomas are the most common primary tumors of the central nervous system (CNS) in adults representing about one third of central nervous system tumors and 81 % of all malignant CNS tumors reported in the United States [1]. The most common and most malignant type of glioma is glioblastoma (GBM), with a median overall survival (OS) rate of 15 months after surgical resection followed by adjuvant radiotherapy (RT) and Temozolomide (TMZ) chemotherapy. The prevalence of GBM is highest in patients aged 50 years or older and is likely to increase with the ongoing demographic shift toward older ages [2].

Well-known postitive prognostic factors for OS in GBM patients are young age at diagnosis, high Karnofsky performance score (KPS), great extent of neurosurgical resection, O-6-methylguanine-DNA methyltransferase- gene (MGMT) methylation as well as isocitrate dehydrogenase (IDH) 1-mutational status [3–5]. Current standard of care for newly diagnosed GBM comprises maximal safe resection, adjuvant radiotherapy with (RT) with concurrent TMZ and post-RT TMZ chemotherapy [6, 7]. Fractionated RT to the tumor bed in 30 fractions of 2 Gy in single doses of 2 Gy to a total accumulated dose of 60 Gy delivered over the course of 6 weeks has been widely accepted as the standard fractionation regimen, balancing effectiveness with radiation toxicity. Recently some authors have suggested hypofractionated regimens for the elderly and frail patient population [8, 9] other authors have evaluated the role of hypofractionation plus TMZ [10].

Other authors have examined the potential role of hyperfractionated- (HFRT) and accelerated hyperfractionated radiotherapy (AHFRT) as well as the role of protons in GBM [11]. The use of HFRT and AHFRT is based on a hypothesized reduction of late radiation injury and prevention of tumor repopulation in treatment intervals [12].

* Correspondence: david.kaul@charite.de
†Equal contributors
Klinik für Radioonkologie und Strahlentherapie, Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany

Despite plausible rationales, various trials have failed to prove the superiority of dose-escalated HFRT and AHFRT in the pre-TMZ era [13].

In 1994, the European Organization for the Research and Treatment of Cancer (EORTC) reported an AHFRT dose escalation trial using doses of 42–60 Gy in 2 Gy fractions three times daily, which failed to show differences in survival in all groups. No additional chemotherapy was used [13]. In 1999 Lutterbach et. al. showed survival rates for 1.5 Gy thrice daily to 54 Gy comparable to conventional RT, again no chemotherapy was used [14]. In 2001 Prados et. al. showed data for AHFRT with or without difluromethylornithine (DFMO) vs. conventional irradiation with or without DFMO with no OS benefit for the experimental groups [15].

The RTOG 83–02 study tested HFRT (2 × 1.2 Gy to doses of 64.8, 72, 76.8, or 81.6 Gy) vs. AHFRT (2 ×1.6 Gy to doses of 48 or 54.4 Gy), all groups received concurrent bis-chloroethyl (BCNU). Contrary to the other aforementioned studies HFRT patients who had received higher doses of 76.8 and 81.6 Gy showed superior survival compared to the AHFRT groups [16].

In summary, the data on HFRT and AHFRT mainly stem from the pre-TMZ era and are not fully conclusive. We therefore want to present experience from our institution on the treatment of patients with newly diagnosed GBM with AHFRT of 2 × 1.6 Gy to 59,2 Gy and concurrent and sequential Temozolomide following the Stupp regimen. Apart from a potential reduction of tumor repopulation as well as a hypothesized reduced late toxicity rate, the regimen does significantly shorten hospitalization time in a group of patients with highly impaired life expectancy.

Materials and methods

Treatment decisions, patient selection and dose regimens

Starting from 01/2009 patients with resected GBM with organs-at-risk (OAR) in close proximity to the resection cavity were offered adjuvant radio-chemotherapy (RCTx) with single doses of 1.6 Gy twice daily to a total dose of 59.2 Gy (19 days schedule) as an alternative to a conventional fractionation with single doses of 2 Gy up to 60 Gy (30 days schedule, NFRT). Of 131 patients 126 received continuous daily TMZ (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant TMZ (150 mg per square meter for 5 days during each 28-day cycle).

In this study we carried out a retrospective analysis of 64 patients who underwent AHFRT plus TMZ and compared them with 67 patients who underwent NFRT plus TMZ between 02/2009 and 10/2014. Follow-up data were analyzed until 01/2015.

In our institution treatment decisions are based on the votes of an interdisciplinary tumor board. Usually all patients <70 years with a KPS >50 % are offered adjuvant AHFRT + TMZ or NFRT + TMZ. AHFRT + TMZ is offered when OARs such as the optic nerves, chiasm or brainstem would be touched by the CTV and covered by the PTV, and in case that the patient is willing and fit enough to undergo treatment twice daily.

Patients ≥70 yeas of age either receive hypofractionated radiotherapy or TMZ only (depending on MGMT-status).

Stratification, variables and follow-up

Patients were stratified according to fractionation scheme, age, gender, KPS, extent of surgery (biopsy, partial-, gross total resection), MGMT-status, tumor localization (frontal, parietal, temporal, occipital, central) and planning target volume (PTV). Follow-up examinations, including MRI as well as clinical and neurologic examinations were performed at 6–8 week intervals after radiotherapy.

Treatment planning

Target delineation in GBM varies substantially between different institutions and several consensus statements are available. However, an ESTRO-ACROP guideline is available since January 2016 [17]. Adjuvant RCTx was initiated within 4 weeks after surgical resection or stereotactic biopsy. Contrast agent enhanced computed tomography in a thermoplastic mask as well as gadolinium enhanced magnetic resonance imaging (MRI) was performed before RT planning.

Target volumes were based on preoperative and postoperative MRI. The gross tumor volume (GTV) was defined as the summation of the postoperative surgical cavity with or without residual tumor lesion(s) as well as tumor extension on the preoperative T1-weighted gadolinium-enhanced imaging. The diffusion-weighted imaging (DWI) images were also used in the estimation of GTV. The extent of peritumoral edema was not routinely included in the clinical target volume (CTV), however, an all-round GTV margin of 2 cm was mandatory. For the planning target volume (PTV) an additional 0.5 cm margin was added. Intensity-modulated radiation therapy (IMRT) was applied using a 6-MV linear accelerator with multileaf collimators. Until 2012 treatment was performed using step-and-shoot intensity-modulated radiation therapy (IMRT), starting in early 2012 all patients were treated using volumetric arc therapy (VMAT).

Toxicity

Higher grade acute toxicity (≥3°) was analyzed for 90 days post treatment according to CTCAE 4.0.

Formulas and statistics

Overall survival (OS) and progression-free survival (PFS) were calculated from the first day of irradiation

using Kaplan-Meier analysis and the log-rank test. Progression was defined retrospectively by clinical note assessments that included integration of imaging and clinical status. Subgroups were compared using univariable analysis and the Cox proportional hazard model for multivariable analysis. A p-value of less than 0.05 was considered statistically significant. A *p*-value of less than 0.1 was considered a trend. All variables from the univariable analysis were included in multivariable analysis. All statistical analyses were performed using IBM SPSS Statistics 19 (New York, USA).

Results

Patient characteristics

Patient characteristics are shown in Table 1. One hundred thirty-one patients treated for GBM were identified in our retrospective analysis. Sixty-seven were treated with NFRT and 64 patients were treated using AHFRT.

The two groups were well matched in terms of gender, PTV, tumor localization, MGMT-status, extent of surgery, KPS and TMZ treatment and salvage treatment. Median age in the AHFRT group was lower than in the NFRT group ($p < 0.001$).

Table 1 Patient characteristics of the 131 GBM patients analyzed

		Overall Collective		NFRT		AHFRT		*p*-value
		(*n* = 131)		(*n* = 67)		(*n* = 64)		
Median Age (min/max) [y]		61	12/80	63	43/78	59	12/80	$p < 0.001$ (*)
Mean PTV ± sd [ccm]		355	±142	339	±141.4	373	±141.8	$p = 0.17$
		n	%	n	%	n	%	
Gender	m	88	67.2 %	46	68.7 %	42	65.6 %	$p = 0.85$
	f	43	32.8 %	21	31.3 %	22	34.4 %	
Localization	Frontal	42	32.1 %	16	23.9 %	26	40.6 %	$p = 0.38$
	Parietal	31	23.7 %	17	25.4 %	14	21.9 %	
	Temporal	38	29.0 %	22	32.8 %	16	25.0 %	
	Occipital	9	6.9 %	4	6.0 %	5	7.8 %	
	Central	9	6.9 %	6	9.0 %	3	4.7 %	
	n/a	2	1.5 %	2	3.0 %	0	0.0 %	
MGMT-status	unmethylated	63	48.1 %	32	47.8 %	31	48.4 %	$p = 0.66$
	methylated	43	32.8 %	23	34.3 %	20	31.3 %	
	n/a	25	19.1 %	12	17.9 %	13	20.3 %	
Extent of surgery	Biopsy	16	12.2 %	6	9.0 %	10	15.6 %	$p = 0.38$
	Partial resection	57	43.5 %	28	41.8 %	29	45.3 %	
	Gross tumor resection	51	38.9 %	29	43.3 %	22	34.4 %	
	n/a	7	5.3 %	4	6.0 %	3	4.7 %	
KPS	50 %	7	5.3 %	4	6 %	3	4.7 %	$p = 0.3$
	60 %	49	37.4 %	27	40 %	22	34.4 %	
	70 %	47	35.9 %	24	36 %	23	35.9 %	
	80 %	28	21.4 %	12	18 %	16	25.0 %	
Temozolomide	yes	126	96.2 %	65	97.0 %	61	95.3 %	$p = 0.68$
	no	5	3.8 %	2	3.0 %	3	4.7 %	
Salvage treatment	Re-irradiation	20	15.3 %	12	17.9 %	8	12.5 %	
	Chemotherapy (tmz)	45	34.4 %	24	35.8 %	21	32.8 %	
	Chemotherapy (other)	6	4.6 %	3	4.5 %	3	4.7 %	
	Bevacizumab	11	8.4 %	5	7.5 %	6	9.4 %	
	Imatinib	1	0.8 %	0	0.0 %	1	1.6 %	
	Dendritic cell vaccination	1	0.8 %	1	1.5 %	0	0.0 %	

NFRT normofractionated radiotherapy, *AHFRT* accelerated hyperfractionated radiotherapy, *PTV* planning target volume, *n/a* not applicable, *MGMT* O-6-methylguanine-DNA methyltransferase, *KPS* Karnofsky performance status, *tmz* temozolomide

Table 2 Univariable analysis of potential preditive factors of progression-free survival

	Univariable analysis				Multivariable analysis		
Variable	HR	95 % CI	*p*	Median PFS [m]	HR	95 % CI	*p*
Age (< vs. > = median of 61 years)	1.08	0.75–1.55	0.69	6 vs. 6	–	–	–
Gender (m vs. f)	0.68	0.46–1.01	0.05	6 vs. 9	0.57	0.35–0.92	0.022 (*)
KPS (< vs. > = median of 70 %)	0.5	0.34–0.72	<0.001 (*)	4 vs. 9	0.5	0.33–0.78	0.002 (*)
MGMT-status (methylated vs. unmethylated)	1.46	0.97–2.2	0.07	9 vs. 6	1.61	1.03–2.52	0.036 (*)
Localization (other vs. central)	1.51	0.76–3	0.24	6 vs. 5	–	–	–
PTV (< vs. > = median of 337 ccm)	1.13	0.79–1.62	0.51	7 vs. 6	–	–	–
Subtotal resection or biopsy vs. gross total resection	0.71	0.49–1.02	0.07	4 vs. 8	–	–	–
Fractionation regimen (NFRT vs. AHFRT)	1.01	0.95–1.01	0.95	7 vs. 6	–	–	–

(*) *p*-value ≤ 0.05, *HR* hazard ratio, *CI* confidence interval, *PFS* progression-free survival, *KPS* Karnofsky performance status, *MGMT* O-6-methylguanine-DNA methyltransferase, *PTV* planning target volume, *NFRT* normofractionated radiotherapy, *AHFRT* accelerated hyperfractionated radiotherapy

Progression-free survival

Median PFS was 6 months for the entire cohort (Table 2). For patients treated with NFRT median PFS was 7 months, for patients treated with AHFRT median PFS was 6 months. At 6 months PFS was 56.9 % in the NFRT group and 51.7 % in the AHFRT group. At 12 months PFS was 16.9 % in the NFRT group and 19 % in the AHFRT group, (Fig. 1). There was no difference between both dose regimens in univariable analysis ($p = 0.95$).

Overall survival

Of 131 patients analyzed 107 had died at the time of analysis (01/2015).

Median OS was 13 months for all patients (Table 3). For patients treated with NFRT median OS was 15 months, for patients treated with AHFRT median OS was 10 months. At 12 months OS was 66 % in the NFRT group and 48.2 % in the AHFRT group. At 24 months OS was 14.7 % in the NFRT group and 16.7 % in the AHFRT group (Fig. 2). There was no difference between both dose regimens in univariable analysis ($p = 0.46$).

Prognostic factors

Positive predictors of survival in univariable analysis were female gender, higher KPS, MGMT methylation and gross total resection. In multivariable analysis MGMT methylation and gross total resection remained significant

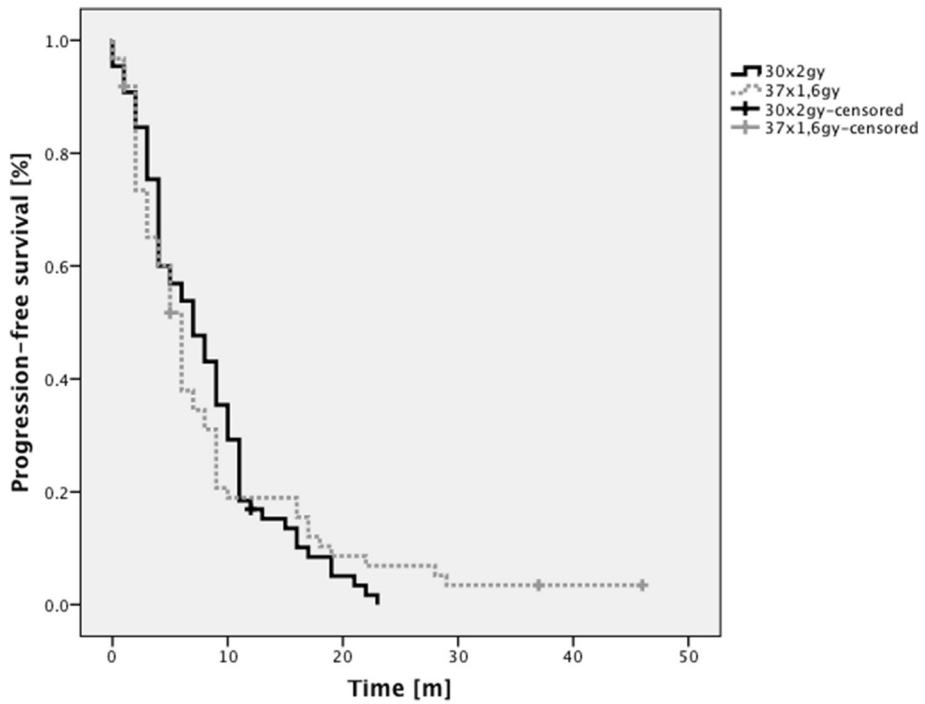

Fig. 1 Kaplan-Meier analysis of PFS rates grouped according to dose regimen. No significant differences were found between both groups

Table 3 Univariable analysis of potential preditive factors of overall survival

	Univariable analysis			Multivariable analysis			
Variable	HR	95 % CI	*p*	Median OS [m]	HR	95 % CI	*p*
Age (< vs. > = median of 61 years)	1.18	0.8–1.7	0.4	14 vs. 12	–	–	–
Gender (m vs. f)	0.62	0.4–0.95	0.028 (*)	11 vs. 16	0.64	0.38–1.08	0.095
KPS (< vs. > = median of 70 %)	0.96	0.94–0.98	<0.001 (*)	9 vs. 15	–	–	–
MGMT-status (methylated vs. unmethylated)	1.68	1.08–2.61	0.021 (*)	16 vs. 11	1.89	1.158–3.09	0.011 (*)
Localization (other vs. central)	1.71	0.83–3.56	0.15	13 vs. 13	–	–	–
PTV (< vs. > = median of 337 ccm)	1.37	0.93–2.02	0.11	14 vs. 12	1.61	1–2.6	0.048 (*)
Subtotal resection or biopsy vs. gross total resection	0.64	0.43–0.95	0.025 (*)	11 vs. 15	0.62	0.39–0.98	0.041 (*)
Fractionation regimen (NFRT vs. AHFRT)	1.16	0.79–1.71	0.46	15 vs. 10	–	–	–

(*) *p*-value ≤ 0.05, *HR* hazard ratio, *CI* confidence interval, *OS* overall survival, *KPS* Karnofsky performance status, *MGMT* O-6-methylguanine-DNA methyltransferase, *PTV* planning target volume, *NFRT* normofractionated radiotherapy, *AHFRT* accelerated hyperfractionated radiotherapy

predictors, the factor "smaller PTV" became significant in multivariable analysis. Gender and lower KPS were not significant in multivariable analysis.

The fractionation regimen was not a predictor of survival in univariable- or multivariable analysis.

Subgroup analysis according to predictive factors did not reveal any specific group to benefit from either NFRT compared to AHFRT or vice versa (Table 4).

Toxicity

All patients in both groups completed radiotherapy. All patients scheduled for concurrent chemotherapy (126/131) completed concurrent TMZ. In the normofractionated group seven patients did not complete post-radiotherapy TMZ due to neutropenia or thrombocytopenia. In the hyperfractionated group 3 patients did not complete post-radiotherapy TMZ due to neutropenia or thrombocytopenia.

There was no difference in acute toxicity profiles between the two treatment groups. There were seven grade 3 and six grade 4 events in the normofractionated group (grade 3 events: 1 × headache, 2 × neurological, 3 × neutropenia, 1 × thrombocytopenia. Grade 4 events: 2 × neutropenia and 4 × thrombocytopenia).

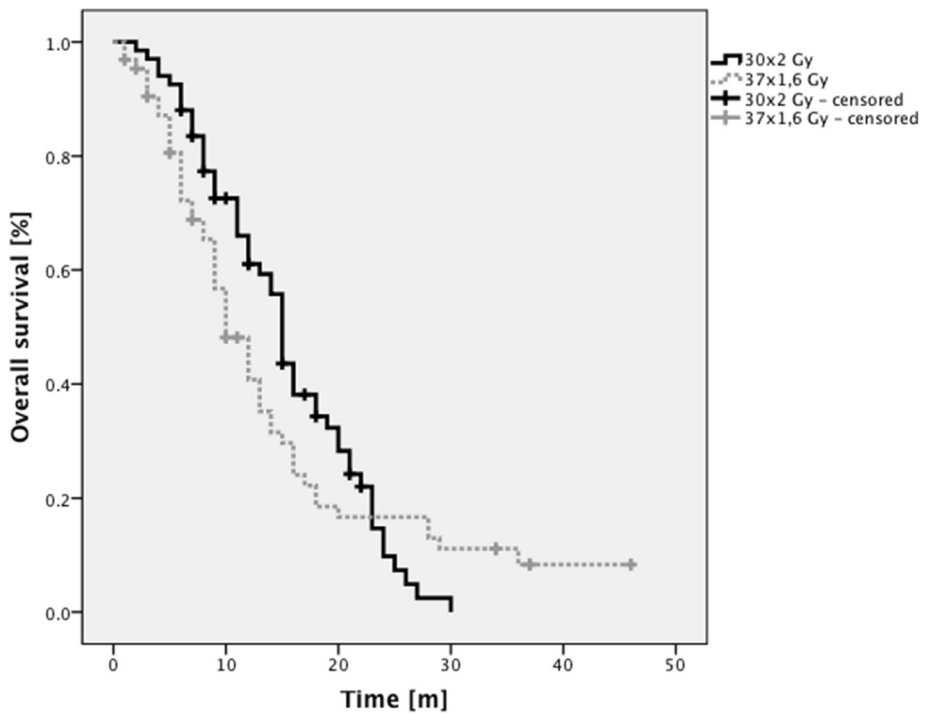

Fig. 2 Kaplan-Meier analysis of OS rates grouped according to dose regimen. No significant differences were found between both groups

Table 4 Subgroup analysis of potential preditive factors of overall survival did not identify any specific subgroup to benefit from either NFRT compared to AHFRT or vice versa

		Median OS [m]		
		NFRT	AHFRT	*p*
Variable				
Age	< median of 61 years	15	12	0.66
	> = median of 61 years	15	9	0.28
Gender	m	14	9	0.31
	f	16	14	0.98
KPS	< median of 70 %	12	6	0.16
	> = median of 70 %	15	13	0.67
MGMT-status	methylated	16	15	0.73
	unmethylated	14	9	0.09
Localization	other	15	10	0.41
	central	9	17	0.44
PTV	< median of 337 ccm	15	12	0.82
	> = median of 337 ccm	15	9	0.24
Extent of resection	Subtotal resection or biopsy	13	8	0.14
	gross total resection	15	13	0.6

KPS Karnofsky performance status, *MGMT* O-6-methylguanine-DNA methyltransferase, *PTV* planning target volume, *NFRT* normofractionated radiotherapy, *AHFRT* accelerated hyperfractionated radiotherapy

In the hyperfractionated group there were two grade 3 events and six grade 4 events (grade 3 events: 1 × neurological, 1 × nausea/vomiting. Grade 4 events: 3 × neutropenia, 3 × thrombocytopenia).

Discussion

Survival

Most studies on hyperfractionation and accelerated hyperfractionation stem from the pre-TMZ era, comparability of PFS and OS rates is thus limited. In our study median OS was 13 months for all patients, 15 months for patients treated using NFRT and 10 months for patients treated with AHFRT. Univariable and multivariable analysis did not show significant differences between the fractionation regimens. This is worthwile to know, because an AHFRT-regimen with 3.5 weeks overall treatment time was capable to equalize the OS-results of the classical 6 weeks treatment. Bearing in mind the limited prognosis of these patients the dose-intensified treatment is a clear benefit.

One of the first studies on AHFRT in GBM was published in 1994 by González et al. who used doses of 42–60 Gy in 2 Gy fractions three times a day. Median survival was 8.7 ± 0.7 months and no statistically significant differences were found for the four different dose-level groups [13].

Lutterbach et. al. published median OS rates of 8.8 months for 1.5 Gy thrice daily to 54 Gy [14].

In 2001 Prados et al. published survival rates of patients treated with AHFRT ± DFMO vs. conventional irradiation ± DFMO with no OS benefit for the experimental groups (8.6–9.8 months) [15].

Werner et al. published the RTOG 83–02 data in 1996, patients received HFRT (2 × 1.2 Gy to doses of 64.8, 72, 76.8, or 81.6 Gy) vs. AHFRT (2 ×1.6 Gy to doses of 48 or 54.4 Gy), all groups received concurrent BCNU. Contrary to the other aforementioned studies HFRT patients who had received higher doses of 76.8 and 81.6 Gy showed superior survival compared to the AHFRT groups. The authors found median OS rates between 10.8 and 12.7 months [16].

In 2005 Stupp et al. published data demonstrating a survival benefit for GBM patients that received concurrent Temozolomide with postoperative radiation, with median survival of 14.6 months for patients receiving concurrent therapy versus 12.1 months for patients who received only radiotherapy [7]. This treatment has since become the standard of care for primary GBM and is referred to as the "Stupp regimen" in everyday clinical routine.

OS rates for all patients of 13 months as shown here are comparable to the data published by Stupp et al. and we did not find significant differences in OS between AHFRT and NFRT in our patient collective.

Limitations

Our study had several limitations. Firstly, the two groups analyzed were not perfectly matched in terms of age. Secondly, the MGMT-status is unknown in approximately 20 % of patients in both treatment groups. Thirdly, no analysis of chronic toxicity was performed due to the intrinsic uncertainties of retrospective analysis. Fourthly, the number of patients analyzed here in both groups might simply be too low to find significant differences in survival between the both regimens. Fifthly, patients with GBM in close proximity to the brainstem were more likely to receive AHFRT, potentially biasing OS rates.

Conclusions

The role of AHFRT in the TMZ era remains unclear. The potential benefits are a reduction of tumor repopulation as well as reduced late toxicity. Other benefits are immanent; the regimen does significantly shorten hospitalization time in a patient collective with highly impaired life expectancy. We propose that the role of AHFRT + TMZ should be further examined in future prospective trials.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions
DK drafted the manuscript, performed statistical analysis and supervised the discussion of the manuscript. JF helped drafting the manuscript, collected data and helped with statistical analysis. HB planned the study and took part in the discussion of the manuscript. AG, PG and SB took part in the discussion of the manuscript. VB planned the study and helped drafting the manuscript. All authors approved the final version of this manuscript.

Received: 11 February 2016 Accepted: 10 May 2016
Published online: 21 May 2016

References

1. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, Stroup NE, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. Neuro Oncol. 2013;15 Suppl 2:ii1–56.
2. Paszat L, Laperriere N, Groome P, Schulze K, Mackillop W, Holowaty E. A population-based study of glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2001;51:100–7.
3. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg. 2001;95:190–8.
4. Bauchet L, Mathieu-Daude H, Fabbro-Peray P, Rigau V, Fabbro M, Chinot O, Pallusseau L, Carnin C, Laine K, Schlama A, et al. Oncological patterns of care and outcome for 952 patients with newly diagnosed glioblastoma in 2004. Neuro Oncol. 2010;12:725–35.
5. Leu S, von Felten S, Frank S, Vassella E, Vajtai I, Taylor E, Schulz M, Hutter G, Hench J, Schucht P, et al. IDH/MGMT-driven molecular classification of low-grade glioma is a strong predictor for long-term survival. Neuro Oncol. 2013;15:469–79.
6. Keles GE, Anderson B, Berger MS. The effect of extent of resection on time to tumor progression and survival in patients with glioblastoma multiforme of the cerebral hemisphere. Surg Neurol. 1999;52:371–9.
7. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987–96.
8. Malmstrom A, Gronberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, Abacioglu U, Tavelin B, Lhermitte B, Hegi ME, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol. 2012;13:916–26.
9. Roa W, Kepka L, Kumar N, Sinaika V, Matiello J, Lomidze D, Hentati D, Guedes de Castro D, Dyttus-Cebulok K, Drodge S, et al. International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme. J Clin Oncol. 2015;33:4145–50.
10. Chen C, Damek D, Gaspar LE, Waziri A, Lillehei K, Kleinschmidt-DeMasters BK, Robischon M, Stuhr K, Rusthoven KE, Kavanagh BD. Phase I trial of hypofractionated intensity-modulated radiotherapy with temozolomide chemotherapy for patients with newly diagnosed glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2011;81:1066–74.
11. Mizumoto M, Tsuboi K, Igaki H, Yamamoto T, Takano S, Oshiro Y, Hayashi Y, Hashii H, Kanemoto A, Nakayama H, et al. Phase I/II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2010;77:98–105.
12. Withers HR, Peters LJ, Thames HD, Fletcher GH. Hyperfractionation. Int J Radiat Oncol Biol Phys. 1982;8:1807–9.
13. Gonzalez DG, Menten J, Bosch DA, van der Schueren E, Troost D, Hulshof MC, Bernier J. Accelerated radiotherapy in glioblastoma multiforme: a dose searching prospective study. Radiother Oncol. 1994;32:98–105.
14. Lutterbach J, Weigel P, Guttenberger R, Hinkelbein W. Accelerated hyperfractionated radiotherapy in 149 patients with glioblastoma multiforme. Radiother Oncol. 1999;53:49–52.
15. Prados MD, Wara WM, Sneed PK, McDermott M, Chang SM, Rabbitt J, Page M, Malec M, Davis RL, Gutin PH, et al. Phase III trial of accelerated hyperfractionation with or without difluromethylornithine (DFMO) versus standard fractionated radiotherapy with or without DFMO for newly diagnosed patients with glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2001;49:71–7.
16. Werner-Wasik M, Scott CB, Nelson DF, Gaspar LE, Murray KJ, Fischbach JA, Nelson JS, Weinstein AS, Curran WJ, Jr. Final report of a phase I/II trial of hyperfractionated and accelerated hyperfractionated radiation therapy with carmustine for adults with supratentorial malignant gliomas. Radiation Therapy Oncology Group Study 83–02. Cancer. 1996;77:1535–43.
17. Niyazi M, Brada M, Chalmers AJ, Combs SE, Erridge SC, Fiorentino A, Grosu AL, Lagerwaard FJ, Minniti G, Mirimanoff RO, et al. ESTRO-ACROP guideline "target delineation of glioblastomas". Radiother Oncol. 2016;118:35–42.

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der Elektronischen Version meiner Arbeit nicht veröffentlicht.

7 Publikationsliste

Publikationen:

1. Kaul, D., Florange, J., Badakhshi, H., Grün, A., Ghadjar, P., Exner, S., Budach, V., Accelerated hyperfractionation plus temozolomide in glioblastoma. Radiat Oncol, 2016. 11: p. 70.

8 Danksagung

Ich danke Herrn Prof. Dr. med. Dr. h.c. Volker Budach, dem Leiter der Klinik für Radioonkologie und Strahlentherapie der Charité, Berlin, für die Möglichkeit, die vorliegende Promotion an seinem Institut durchzuführen.

Mein Dank gilt weiterhin Herrn PD Dr. med. Harun Badakhshi für seine Hilfe bei der Planung dieser Arbeit, seinen Anregungen im Verlauf des Entstehens und seiner Geduld mit seinem Doktoranden.

Ganz besonders möchte ich Herrn Dr. med. David Kaul danken, dessen Expertise bezüglich der technischen und formalen Aspekte zum erfolgreichen Abschluss unserer Publikation und schließlich meiner Promotion geführt haben.

Weiterhin möchte ich meiner Familie danken, die mir mein Medizinstudium ermöglichte, mir den nötigen Rückhalt in allen Situationen gab und mich zu jedem Zeitpunkt ihr Vertrauen spüren ließ.

Meiner Frau Theresa danke ich für ihre unermüdliche und liebevolle Unterstützung.